Title: Prioritizing and selecting pharmaceuticals to test the read-across approach: using human clearance rates to predict biotransformation in fish.

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Abstract:

Many active pharmaceutical ingredients (APIs) have been detected in aquatic systems around the world. These systems typically receive continual municipal sewage inputs, which results in pseudo-persistent exposures of aquatic animals to APIs, thus enhancing their bioaccumulative potential and possibility for adverse effects. Thousands of APIs exist, so full chemical and toxicological assessments are impractical and present a cost and logistical impasse. Further, limited information on bioaccumulation of pharmaceuticals in fish exists. We developed an effects-based prioritization scheme for APIs leveraging available mammalian pharmacokinetic (PK) data to predict biotransformation rates in fish. We collated a database of referenced mammalian PK data to be used strategically for our prioritization method. The method can be used to prioritize drugs based on a single or multiple PK parameters. To predict biotransformation rates in fish, human clearance values were identified for 875 pharmaceuticals. Human clearance values for the selected APIs ranged from 0.0037 to 1070 ml/min/kg. APIs with the slowest clearance were assumed to present the greatest potential for bioaccumulation in fish. Human clearance values were rank-regressed to form a probabilistic distribution. To evaluate the read-across assumptions (slow clearance = high bioaccumulation potential) three groups of APIs were derived. These groups represent high (>90th centile; slowest clearance: 0.0037 0.4 mg/min/kg), median (45th 55th centile; median clearance: 2.9 4.4 mg/min/kg) and low (<10th centile; fastest clearance: 31 1070 mg/min/kg) hazard potential based on centile. Each group initially contained ~100 APIs, which was reduced in a step-wise process. First the APIs with reported renal clearance in humans were excluded, to ensure more direct read-across. Next, priority was given to those compounds with known interactions with hepatic xenobiotic metabolizing enzymes (CYP1A or 3A) in humans relative to the presence of similar enzymes in fish. This resulted in 12 APIs grouped based on hazard potential for biotransformation studies: high - dutasteride, fluconazole, phenobarbital, phenytoin; medium dexamethasone, spironolactone, gemfibrizol, chloroquine; and low propofol, praziquantel, dextromethorphan, hydralazine. As described in a companion poster, predictions of bioaccumulative potential will be validated for the selected APIs using trout S9 substrate depletion method.